Post-Transfusion Hepatitis

A Serious Clinical Problem

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■ *Serum hepatitis and infectious hepatitis may have a common pathogen and their few clinical differences the result only of a difference in portal of entry.*

The risk of serum hepatitis from transfusions derived from prison and Skid Row populations is at least 10 times that from the use of volunteer donors. For every 100 patients receiving a single transfusion, the attack rate is 0.3 per cent when the donor is of the family or volunteer type and 3.2 per cent when the donor is from a prison or Skid Row population.

The most practical methods of reducing the hazard of serum hepatitis from blood are to limit the use of blood by giving one transfusion instead of two, two instead of three, etc., and especially by excluding, if possible, all prison and Skid Row donors.

It is urged that state and federal control of the quality of blood used for blood transfusions be studied with the possibility that measures may be taken to increase its safety. If it is necessary that blood from prison and Skid Row donors be used to meet the demands, such blood should be labeled as carrying a significantly increased hazard of transmitting serum hepatitis in order that the physician prescribing blood may take the necessary precautions.

SERUM HEPATITIS is a clinical entity that may or may not be related to or caused by the viruses or family of viruses that cause infectious hepatitis. In many ways, the similarities between these two entities are so striking that the temptation is to consider their differences more a manifestation of portal of entry than of variances inherent in similar but not identical infectious agents. Perhaps they are.

The data contained in this review pertain to a 10-year study (1945-56) conducted at the University of Chicago Clinics. The number of patients transfused with blood during that period was 12,598 and they received a total of 42,407 units of blood. This was a continuing study and some of the basic details are shown in Table 1. From an adjusted 21 per cent sample of these patients other studies were carried out and published elsewhere.[1] The study was completed before cardiac bypass procedures were instituted at that hospital.

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Epidemiology of Serum Hepatitis

Age Distribution. In most reports it is shown that approximately 85 per cent of cases of infectious hepatitis occur in patients under the age of 25. Because the infectious agent is ubiquitous, presumably there are many anicteric, asymptomatic cases of infectious hepatitis that are never

TABLE 1.—*Blood Transfusions and Cases of Serum Hepatitis (1946-1956)*

Number of patients transfused*	12,598
Number of units of blood given	42,407
Average number of units per patient	3.4
Completeness of followup	92.0%
Number of observed cases: icteric serum hepatitis	189
Number of known deaths from serum hepatitis	21

*Of these 12,598 patients, 11,627 are separate and independent patients in that they received no additional series (episodes) of blood transfusions during the period of study; 971 did have two or more series of transfusions.

TABLE 3.—*Effect of Sex-Linked Indications for Blood Transfusion Upon Serum Hepatitis, by Age and Sex of Patients*

	All Cases	*Sex-Linked Transfusions*	*Non-Sex-Linked Transfusions*
Female	104	31	73
Male	85	4	81
Totals	189	35	154

Age Distribution

	0-19	*20-49*	*50-59*	*60-69*	*70 and Older*
Female	6	52	21	20	5
Male	6	21	26	23	9

diagnosed, and thus most people probably have some degree of immunity before the age of 25. In contrast, the majority of patients receiving blood transfusions are middle-aged or older, since the need for transfusion increases with age, as does the average number of transfusions given. For this reason, 75 per cent of the cases of icteric serum hepatitis were observed among patients over the age of 39 (Table 2).

Sex Factor. Sex of the patient does not influence the numbers of cases of hepatitis except that there are three sex-linked reasons for giving transfusions to female patients and one sex-linked reason for transfusions to males. These are childbirth, mastectomy and pelvic operations in women, most of which occur between ages 20 and 50. In males, prostatectomy is the sex-linked operation often requiring transfusion, and for the most part it is performed after age 50. When the cases of icteric hepatitis resulting from sex-linked reasons for transfusion are eliminated, the remaining numbers of cases of hepatitis are essentially equally distributed (Table 3).

Incubation Period. The length of incubation period has long been used as one method for distinguishing infectious hepatitis from serum hepatitis. It is true that jaundice develops within three to four weeks in most patients exposed to the pathogen orally. In serum hepatitis, jaundice may occur as early as the fourth week after transfusion and as late as the thirtieth week but three fourths of the cases occur between 30 and 90 days after transfusion, and half the cases occur before the sixtieth day (Table 4). These incubation periods are much shorter than they were originally thought to be, when cases occurring after the sixtieth day were arbitrarily considered serum hepatitis. The difference in length of incubation periods, while real, may not necessarily imply that two distinct infectious agents are involved. It may be that the variations in incubation time can be accounted for by the different portal of entry.

Interrelationships of Serum Hepatitis and Infectious Hepatitis. These things seem clearly established. First, that a fecal ultrafiltrate from a patient in the active stages of infectious hepatitis ingested by a susceptible person (Patient A) will result in a case of infectious hepatitis, usually within three to four weeks. If, however, this same filtrate is given parenterally to a susceptible person (Patient B), hepatitis of a variety similar to, if not identical

TABLE 2.—*Age Distribution, by Number and Per Cent, of Transfused Patients and of Patients Acquiring Icteric Hepatitis*

Age Groups	*Number of Patients in Age Groups*	*Per Cent of Patients in Age Groups*	*Number of Cases of Icteric Hepatitis*	*Per Cent of Cases of Icteric Hepatitis by Age Groups*
Under 1 year	642	5.1	2	1.1
1-9	768	6.1	3	1.6
10-19	516	4.1	7	3.7
20-29	1,423	11.3	7	3.7
30-39	1,959	15.5	29	15.1
40-49	2,365	18.8	37	19.6
50-59	2,431	19.3	47	24.9
60-69	1,828	14.5	43	22.9
70 and over	666	5.3	14	7.4
Total	12,598	100.0	189	100.0

TABLE 4.—*Incubation Period of Serum Hepatitis from Blood Transfusion*

	Incubation Periods in Days						
	10-29	*30-59*	*60-89*	*90-119*	*120-149*	*180-248*	*Total*
Cases among all patients transfused	4	78	54	23	15	15	189
Per cent of total cases by incubation period	2.2	41.1	28.7	12.0	8.0	8.0	100.0
Cases among patients when all transfusions given within one day	0	44	23	10	6	3	86
Per cent by incubation period	0	51.2	26.6	11.8	7.0	3.4	100.0
Cases among patients when all transfusions given within 3 days	2	57	29	13	8	4	113
Per cent by incubation period	1.8	50.4	25.6	11.4	7.1	3.7	100.0

with, serum hepatitis will develop in 30 days to six months. Second, Patient B, with the delayed form of hepatitis, even though his infection is derived from an ultrafiltrate of a primary case (Patient A) of infectious hepatitis, differs in that ultrafiltrates of his feces and urine, prepared during the active stages of his disease, will not induce hepatitis when given orally or parenterally to other persons.

However, if the blood or any of its icterogenic fractions from Patient A and Patient B are given parenterally to Patients C and D, both of these individuals, if susceptible, will in time have the delayed form of the disease—serum or transfusion-associated hepatitis. But, if the viremic blood from Patients A and B is administered orally, it will not produce hepatitis. It thus appears that the agent responsible for both entities is that which causes infectious hepatitis and that once this agent enters the bloodstream from the alimentary tract, it is in some way altered so that it is infectious only when administered parenterally. Nonetheless, the ultrafiltrates from the stool of Patient A remain infectious if administered orally.

It therefore appears that the virus of infectious hepatitis, once ingested, is readily transported from the alimentary tract to the circulation, but the agent, once in the bloodstream, does not return to the alimentary tract, at least not in a form that renders the stool infectious. Viremic blood apparently is infectious only when administered parenterally, not orally. It is also of interest that the blood of the patient with infectious hepatitis remains infectious long after the ultrafiltrate of his stool has lost its capacity to infect when given orally or parenterally. It appears therefore that the viremic "carrier" presented no problem until jennerian vaccination was introduced in 1798, a procedure which for 90 years entailed the preparation of the vaccine by harvesting and pooling the purulent lymph of people vaccinated with cow pox. Once Copeman's method, in which the vaccine was cultivated on the skin of the calf, was introduced, the need for the human harvest disappeared and so did the occasional epidemic of jaundice associated with the jennerian-type vaccination.

With Ehrlich's introduction of a new treatment for syphilis in 1910, many of the epidemics of jaundice which followed were erroneously attributed to the heavy metals used, particularly his arsphenamines. (So abusive to Ehrlich were these criticisms that they may have contributed to his untimely death.) Not until 1942 was it generally recognized that these epidemics were due to the use of the multiple dose syringe and to improper sterilization of needles and syringes, although in 1920 Stokes had clearly indicated that jaundice associated with arsenical therapy was related to the blood of patients recovering from infectious hepatitis and was not caused by the drugs used.

The precautionary measures against viral hepatitis are of two kinds. One is strict isolation of the patient with infectious hepatitis until he has recovered clinically. No such measure is necessary for patients with serum hepatitis, although it may be advisable if the source of the infection is in question. However, in these latter patients, care must be taken to dispose of or to autoclave all equipment used for the drawing and testing of blood samples. The second precautionary measure relates to these persons when, after they recover from hepatitis, they wish to serve as blood donors. As such they are a potential source of infection to patients receiving their blood or its icterogenic products. At times the disease may be transmitted accidentally from viremic blood contained in syringes and glassware that may puncture the skin, as occasionally occurs among workers in blood laboratories. Aside from these general precautions, the use of gamma globulin is advisable, usually 5 to 10 ml on days 7, 21 and 35.[1]

The Carrier-Donor

Occult Carriers. The viremic donor is the vector in serum hepatitis and, because his carrier state cannot be recognized by present laboratory methods, his menacing presence can only be determined when hepatitis develops in a patient receiving his blood and the diagnosis is reported to the blood bank, thereby identifying the donor, if suitable records are maintained. This carrier appears decidedly different from the patient recovering from viral hepatitis, whose viremic state lasts only for a few months to possibly a year or so.

The viremic carrier, whose blood is drawn at the blood bank and causes hepatitis when given to a susceptible patient, almost certainly has been carefully questioned and has reported that insofar as he knows he has never had this disease. Almost certainly in the case of the volunteer donor, the information he gives is correct and he is quite innocent of any knowledge that he has had hepatitis or that he has been a carrier of the virus. If, at this time, all practical tests of liver function were to be performed, the results would not differ from those in the normal population.* Moreover, if one keeps such carriers under observation for years, icteric hepatitis appears not to develop later, yet their viremic state may continue indefinitely; if they serve as donors a second time some years later, their blood, when given to susceptible patients, may again result in cases of icteric hepatitis. It is possible that such a carrier may remain viremic for life, but he poses no threat to others if he is aware of his condition and does not serve as a blood donor, or if, in a physician's office or hospital, he is not given parenteral medication from a multiple-dose vial or syringe subsequently used, without proper sterilization, for inoculating other patients.

In short, the carrier who is so dangerous from the standpoint of transfusion appears to have established a state of indifference or tolerance to the virus and to be in good health, living in a completely compatible relationship with the organism. One can only speculate how such a harmonious coexistence can develop—from the standpoint of the host, as well as that of the virus. Several events which normally would occur, possibly in the carrier, do not. Ordinarily a virus replicates within the cell, often a specific cell. It continues this process and as antibodies are formed the cellular structure is destroyed in the course of antigen-antibody reaction. Indeed, it is this reaction which appears to create symptomatic disease. When, however, no antibody is produced, the animal appears healthy and capable of living most if not all of its lifespan in this state of harmonious tolerance. The conditions under which this degree of tolerance has been established experimentally may not be the same conditions in which the carrier state is established in man, although they could be. In animals, the state apparently does not develop unless the species is infected late in the gestational period, or in the early prenatal period, before the animal is able to produce antibodies. This same mechanism possibly could occur in man and account for the carrier-donor, but we do not really know.

*Drug addicts and patients with chronic liver disease may have subacute and chronic states of viral hepatitis, in which case results of tests of liver function are usually abnormal and to some degree the patients may be symptomatically ill.

Risk Rates of Contracting Serum Hepatitis from Blood

What is the probability that receiving a transfusion of a single unit of blood will cause icteric or clinically apparent hepatitis to develop in the patient? Several factors contribute. First, the evidence is clear that some icterogenic products are more virulent than others; that is, some will produce a higher attack rate than others. Thus a patient with some degree of immunity may not get icteric hepatitis from a product that causes jaundice in patients with less immunity. Therefore, the blood of a particular carrier may produce icteric hepatitis in one patient and not in another. Second, it appears that the proportion of susceptible patients is remarkably constant among similar population groups exposed to a common icterogenic agent. If exposed to a common agent of greater icterogenicity, this uniformity among subgroups is reflected throughout each group by an increase in the attack rates, as illustrated in Table 5.

Clearly, then, two important considerations which we know exist but cannot identify in relation to a specific donor or specific patient, are the degree of resistance of the patient and the degree of infectivity or virulence of the donor's blood. Only if the virulence of the carrier-donor's blood is sufficient to overcome the patient's resistance will a case of icteric hepatitis develop.

There are groups among donor populations whose blood produces more cases of icteric hepatitis than other groups. For example, the number of cases resulting from single transfusions when

TABLE 5.—*Observed Attack Rates Among Isolated Subgroups of Normal Recipients of Aliquots from Common Lots of Pooled Icterogenic Plasma*

Number of Recipients in Subgroups	*Cases of Serum Hepatitis*	*Attack Rates (Per Cent) in Subgroups*
	Lot No. 335	
26	6	23.1
64	15	23.4
65	17	26.2
65	15	23.1
68	21	30.9
74	17	23.0
76	18	23.7
82	21	25.6
84	20	23.8
87	15	17.2
144	34	23.6
182	35	19.2
210	51	24.3
1,227	285	23.2
	Lot No. 338	
63	8	12.7
70	11	15.7
75	12	16.0
76	8	10.5
80	13	16.2
85	11	12.9
449	63	14.0

the donors are of the prison-Skid Row variety is 10 times greater than the number of cases resulting when the donors are volunteers, members of the family or friends (Table 6). This difference is alarming, and it also obtains for multiple transfusions when the donor population is of the prison type. These results may seem striking; however, they have been confirmed by other investigators.[2,3]

One of two factors, or possibly both, would seem to explain this intolerable situation. It may be that the blood of the carrier-donor among the prison-Skid Row population is 10 times more virulent than that of the carrier who is a volunteer or family donor and thus overcomes resistance among patients 10 times more frequently than does the blood of the volunteer carrier-donor. Or perhaps there are 10 times more carriers among the prison-Skid Row population than among the population at large.

Practical Methods for Reducing the Risk

Two practical methods exist at this time whereby the numbers of cases of serum hepatitis from blood transfusions may be reduced. One is a method designed to reduce the attack rate for serum hepatitis by improving the quality of the donor populations used without necessarily reducing the numbers of transfusions given. The second is to reduce the number of units of blood to which each patient is exposed by extending the use of plasma volume expanders. It is essential to pursue both methods. To pursue one without the other will help, but the results will be much more impressive when both measures are actively pressed.

Quality Control of Donor Populations. From the information available to him, it is not possible under most circumstances for the physician prescribing blood for a patient to determine the quality of the population from which the donor comes.

Although most blood banks, as well as the American Red Cross, find it necessary at times to supplement their blood reserves by drawing blood from prison donors, unfortunately there is no indication on the label of the blood container informing the physician whether the blood comes from a high-risk donor population or from a low-risk volunteer group. Until it is required that such information be added to the label, the patient's physician cannot properly assess the risk the transfusion may carry. Without this information, it follows that the physician is unable to justify the extra precautionary measures that are necessary when a donor is from a high-risk group. In addition, when the source of blood is not known, the patient cannot be informed of the magnitude of the potential risk of hepatitis from the blood he is to receive.

TABLE 6.—*Number of Cases as Related to Source of Blood Transfused*

Source of Blood	*Total Number of Units*	*Number of Patients Transfused*	*Cases of Hepatitis Encountered*	*Number of Transfused Patients per Case of Hepatitis*	*Ratio of Units of Blood per Case*	*Average Number of Units per Patient*
All Prison	5,337	1,854	62	30	86	2.09
Some Prison	9,420	3,247	90	36	105	2.90
No Prison (all volunteer)	27,650	7,497	27	278	1,024	3.69
Total	42,407	12,598	179*			

*From blood purchased, and donors' source not known, an additional 10 cases of icteric serum hepatitis occurred, bringing the total number of cases to 189.

It is a curious fact that with quality control so much a part of the preparation of other biologic products, similar measures have not been taken by federal or state agencies to insure high quality of blood by insisting upon the use of high quality donor populations. This could be done either by the elimination of prison and similar high-risk donor populations or, as suggested above, if these must be used, to have the container in which the blood is supplied carry a special warning. With respect to most if not all other biologic products, state and federal laws require elaborate records to identify the source and quality of the product, its manufacturer and other simple but pertinent details in order that a particular lot or batch may be effectively traced. At present we cannot perform a practicable biological test on a particular unit of blood to detect the presence of a hepatitis virus which would make the unit unfit for transfusion. But we could be informed that the blood obtained from a high-risk donor population will yield approximately 10 times more cases of icteric serum hepatitis than blood derived from a low-risk population. Until the importance of such information is recognized and something is done to provide it, the physician cannot assume his proper role in prescribing blood—namely, to select, when possible, the safest product for his patient.

Reduction in Number of Units of Blood Given per Patient. Because multiple transfusions of blood carry all the risks of a single transfusion multiplied, any method that will safely permit the administration of fewer units of blood will to that extent reduce the patient's exposure risk to serum hepatitis. For example, two transfusions carry twice the risk of one and four transfusions carry essentially twice the risk of two, and so on. It thus becomes just as important to eliminate one transfusion in a patient who would otherwise receive two or three units of blood as it is to eliminate, when possible, the use of the single transfusion.

Benefits of the Single Transfusion

In 1954 it was pointed out that a single transfusion carried a hazard greater than was generally appreciated; and in the particular instance then being discussed, serum hepatitis, which had developed approximately seven weeks after the infusion of one unit because of a transient episode of hypotension during appendectomy under spinal anesthesia, had caused the patient's death. Since a single transfusion was all that was necessary, would not another fluid with less hazard have been adequate in this patient? As to this particular case, the answer is self-evident.

Unfortunately what appeared in retrospect to have been the abuse of the single transfusion in this instance caused many investigators to generalize that all single transfusions were unwarranted. It has been distressing to learn that the Joint Commission on the Accreditation of Hospitals has included in its questionnaire an item regarding the number of patients receiving single transfusions, without inquiring as to the number of patients receiving two or three transfusions. The intent of this question has been misinterpreted, because, upon making inquiries in a number of hospitals in this state and elsewhere, the author learned that the trend is for administrators to exert pressures to curtail the number of patients receiving a single transfusion, with the result that some physicians admit that, to minimize criticism, it is easier to give two or three units than one. Any attempt to reduce the hazards of blood transfusions is laudable, but an attempt such as this one appears to enlarge the problem rather than to reduce it. Much more can be accomplished, however, if blood from a high-risk carrier population be labeled as carrying an increased hazard of serum hepatitis. Single transfusions from the family donor will cause approximately three cases per thousand patients, whereas those from the high-risk population carry a risk of 32 cases per thousand.

The effect of reductions in numbers of blood transfusions upon an actual series of patients transfused is illustrated in Table 7. If it were possible to eliminate one transfusion from each of the 12,598 patients transfused with blood, the total transfused would be reduced by 37.6 per cent, or by 4,738 patients. Of the remaining 7,860 patients, 3,030, or 38.5 per cent, would now receive one transfusion instead of two. Were it possible to eliminate two transfusions from every patient transfused, the number of patients receiving blood would be reduced from 12,598 to 4,830, and the number receiving a single transfusion under these conditions would be 1,561 or 32.0 per cent of the total 4,830 now exposed.

With this reduction in the number of blood transfusions administered per patient, the total number of units of blood given would be reduced by scarcely 20 per cent, whereas the total number of patients exposed to blood would be reduced by more than 60 per cent who thereby would be

TABLE 7.—*Effect of the Elimination of One and Two Transfusions in a Patient Population in a General Hospital*

	Number of Transfusions						
	1	*2*	*3*	*4*	*5*	*6 and more*	*Total*
No. patients transfused	4,738	3,030	1,561	964	574	1,731	12,598
Per cent patients transfused	37.6	24.0	12.4	7.7	4.6	13.7	100.0
No. cases of hepatitis	21	48	26	21	17	46	179
					5 and more		
No. patients transfused if first transfusion were eliminated	3,030	1,561	964	574	1,731		7,860
Per cent patients transfused	38.5	19.9	12.3	7.3	22.0		100.0
No. cases of hepatitis	48	26	21	17	46		158
				4 and more			
No. patients transfused if first two transfusions were eliminated	1,561	964	574	1,731			4,830
Per cent patients transfused	32.0	20.0	12.0	36.0			100.0
No. cases of hepatitis	26	21	17	46			110

Note: The benefits shown in this table are the results of the elimination of one and two units of blood in patients receiving only one or two units and therefore avoiding blood exposure entirely. No attempt was made to adjust for benefits derived when the first two transfusions are deleted from those receiving three or more units of blood.

spared any risk of serum hepatitis. With these reductions the 69 cases that occurred among recipients of one and two units of blood would have been avoided and probably an additional but indeterminate number would not have occurred among those receiving larger numbers of transfusions.

It can be seen from the above that when blood is used conservatively, and when this conservatism is applied to multiple as well as single-unit recipients, the proportion of single transfusions given in any general civilian hospital will remain at approximately 35 per cent of all transfusions given, excluding blood used for extracorporeal circulation. By use of expanders, properly selected and appropriately administered, the use of blood in many patients now receiving two or even three units could be avoided.

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